(FILE 'HOME' ENTERED AT 18:10:31 ON 17 OCT 2002)

FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, EMBASE, BIOSIS, MEDICONF' ENTERED AT 18:10:38 ON 17 OCT 2002

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L1          82 S MYOBLAST (L) NITRIC OXIDE SYNTHASE
L2          25 S MYOBLAST (L) INDUCIBLE NITRIC OXIDE SYNTHASE
L3           8 DUP REM L2 (17 DUPLICATES REMOVED)
L4           8 SORT L3 PY
L5       28283 S INDUCIBLE NITRIC OXIDE SYNTHASE
L6         685 S L5 AND (PLASMID OR VECTOR)
L7          80 S L6 AND (MUSCLE CELL OR MYOBLAST)
L8          36 S L7 AND PY<=1998
L9          36 SORT L8 PY
L10         13 DUP REM L9 (23 DUPLICATES REMOVED)
L11         13 FOCUS L10 1-
L12         13 SORT L10 PY

=> d an ti so au ab pi l12 1 2 4 5 7 9 10 12 13
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L12 ANSWER 1 OF 13 MEDLINE
AN 96350358 MEDLINE
TI Vascular **inducible nitric oxide synthase** gene therapy: requirement for guanosine triphosphate cyclohydrolase I.
SO SURGERY, **(1996 Aug)** 120 (2) 315-21.
Journal code: 0417347. ISSN: 0039-6060.
AU Tzeng E; Yoneyama T; Hatakeyama K; Shears L L 2nd; Billiar T R
AB BACKGROUND: Human **inducible nitric oxide synthase** (iNOS) gene transfer inhibits myointimal hyperplasia in vitro. However, unstimulated vascular smooth **muscle cells** (SMC) do not synthesize tetrahydrobiopterin (BH4), an essential cofactor for iNOS, which may be an obstacle to successful vascular iNOS gene therapy. We investigated the capacity of gene transfer of guanosine triphosphate (GTP) cyclohydrolase I (GTPCH), the rate-limiting enzyme for BH4 biosynthesis, to supply cofactor for iNOS activity. METHODS: A human GTPCH expression **plasmid** (pCIS-GTPCH) was transfected into rat aortic SMC (RAOSMC) and BH4-deficient NIH3T3 cells engineered to stably express human iNOS (3T3-iNOS). GTPCH activity and intracellular biopterins were assessed as a measure of successful transfection, and the capacity of GTPCH to reconstitute iNOS activity was used to determine whether BH4 was made available to the iNOS protein. RESULTS: The pCIS-GTPCH-transfected 3T3 cells had demonstrable GTPCH activity as compared with control cells (169.3 +/- 6.6 pmol/hr/mg versus 0, $p < 0.001$). Intracellular biopterin levels were also increased in transfected 3T3 and SMC (60.6 +/- 2.6 and 101.7 +/- 28.3 pmol/mg, respectively, versus less than 4 in control cells). GTPCH reconstituted near-maximal iNOS activity in 3T3-iNOS cells despite a gene transfer efficiency of less than 1%. GTPCH and iNOS enzymes did not have to coexist in the same cell for the synthesized BH4 to support iNOS activity. CONCLUSION: GTPCH gene transfer reconstitutes iNOS activity in BH4-deficient cells despite poor transfer efficiency. GTPCH can deliver a cofactor to targeted cells even if it is synthesized in neighboring cells, and may be a means to concurrently deliver BH4 with iNOS in vivo.

L12 ANSWER 2 OF 13 MEDLINE
AN 96295016 MEDLINE
TI Vascular gene transfer of the human **inducible nitric oxide synthase**: characterization of activity and effects on myointimal hyperplasia.
SO MOLECULAR MEDICINE, **(1996 Mar)** 2 (2) 211-25.
Journal code: 9501023. ISSN: 1076-1551.
AU Tzeng E; Shears L L 2nd; Robbins P D; Pitt B R; Geller D A; Watkins S C; Simmons R L; Billiar T R
AB BACKGROUND: Nitric oxide (NO) has been shown to decrease myointimal hyperplasia in injured blood vessels. We hypothesize inducible No synthase (iNOS) gene transfer even at low efficiency will provide adequate local no production to achieve this goal. MATERIALS AND METHODS: A retroviral **vector** containing the human iNOS cDNA (DFGiNOS) was used to transfer the iNOS gene into vascular cells and isolated blood vessels to

answer the following questions: can vascular endothelial and smooth **muscle cells** support iNOS activity and will low efficiency iNOS gene transfer suppress myointimal hyperplasia in injured porcine arteries? RESULTS: DFGiNOS-infected sheep pulmonary artery endothelial cells (SPAEC) expressed significant iNOS mRNA and protein, releasing nitrite levels of 155.0 +/- 10.7 nmol/mg protein/24 h vs. 5.5 +/- 1.1 by control cells. Transduced rat smooth **muscle cells** (RSMC) also expressed abundant iNOS mRNA and protein, but, in contrast to SPAEC, NO synthesis was dependent on exogenous tetrahydrobiopterin (BH4) (291.8 +/- 10.4 nmol nitrite/mg protein/24 hr with BH4, 37.7 +/- 2.6 without BH4). Only porcine arteries infected with DFGiNOS following balloon injury exhibited a 3-fold increase in total NO synthesis and a 15-fold increase in cGMP levels over control vessels in a BH4 dependent fashion, despite only a 1% gene transfer efficiency. Transfer of iNOS completely prevented the 53% increase in myointimal thickness induced by balloon catheter injury; the administration of a NOS inhibitor reversed this effect. CONCLUSIONS: These in vitro findings suggest that vascular iNOS gene transfer may be feasible. Furthermore, a low gene transfer efficiency may be sufficient to inhibit myointimal hyperplasia following arterial balloon injury, although a source of BH4 may be required.

L12 ANSWER 4 OF 13 CAPLUS COPYRIGHT 2002 ACS
AN 1996:435235 CAPLUS
DN 125:76395
TI Amelioration of human erectile dysfunction by treatment with inducible nitric oxide synthetase (iNOS) or NOS-inducing agents
SO PCT Int. Appl., 67 pp.
CODEN: PIXXD2
IN Gonzalez-Cadavid, Nestor F.; Rajfer, Jacob
AB Treatment of erectile dysfunction comprising administering to a patient, **inducible nitric oxide synthase** (iNOS) agents, including penile iNOS, inducers of penile iNOS, iNOS cDNA, or penile smooth **muscle cells** or corpora cavernosa expressing iNOS cDNA is claimed. Typical in vivo treatment involves delivery of these agents to the penile tissue of a patient by const. or intermittent implanted or external infusion pump, pellets intraurethral administration, injection or other related procedures. The genetically engineered cells or penile tissue from the patient hyperexpressing iNOS is implanted in microcapsules, pellets, or other methods, or directly by surgical inoculation into the corpora cavernosa. In certain cases, an oral or injectable systemic route of administration is applicable. Also disclosed are methods of treatment involving in vitro induction of iNOS in cultured smooth **muscle cells** and thereafter delivery of purified or recombinant iNOS enzyme, prodn. of iNOS cDNA and genetic transformation with iNOS cDNA, followed by delivery thereof to the penis of a patient. The methods of this invention include hyperexpression and/or biol. modulation of other endogenous and exogenous NOS isoforms in the penis, for the treatment of erectile dysfunction. Rat penis smooth **muscle cell** iNOS cDNA was cloned and sequenced. Improved erectile response was demonstrated in rats infused with iNOS inducers (such as interferon-.gamma. or interleukin-1.beta.).

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9614748	A1	19960523	WO 1995-US14588	19951109 <--
W: AL, AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KP, KR, LK, LR, LT, LV, MD, MK, MX, NO, NZ, PL, RO, RU, SI, SK, TT, UA, US, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5594032	A	19970114	US 1994-337357	19941110 <--
CA 2204886	AA	19960523	CA 1995-2204886	19951109 <--
AU 9642336	A1	19960606	AU 1996-42336	19951109 <--
AU 693621	B2	19980702		
EP 808104	A1	19971126	EP 1995-940665	19951109 <--
R: DE, FR, GB, IT				
CN 1174493	A	19980225	CN 1995-197487	19951109 <--
JP 11501206	T2	19990202	JP 1995-516199	19951109

L12 ANSWER 5 OF 13 MEDLINE
AN 97434244 MEDLINE

TI Adenoviral transfer of the **inducible nitric oxide synthase** gene blocks endothelial cell apoptosis.
SO SURGERY, **(1997 Aug)** 122 (2) 255-63.
Journal code: 0417347. ISSN: 0039-6060.
AU Tzeng E; Kim Y M; Pitt B R; Lizonova A; Kovesdi I; Billiar T R
AB BACKGROUND: We have previously reported that vascular **inducible nitric oxide synthase** (iNOS) gene transfer inhibits injury-induced intimal hyperplasia in vitro and in vivo. One mechanism by which NO may prevent intimal hyperplasia is by preserving the endothelium or promoting its regeneration. To study this possibility we examined the effect of iNOS gene transfer on endothelial cell (EC) proliferation and viability. METHODS: An adenoviral **vector** (AdiNOS) containing the human iNOS cDNA was constructed and used to infect cultured sheep arterial ECs. NO production was measured, and the effects of continuous NO exposure on EC proliferation, viability, and apoptosis were evaluated. RESULTS: AdiNOS-infected ECs produced 25- to 100-fold more NO than control (AdlacZ) infected cells as measured by nitrite accumulation. This increased NO synthesis did not inhibit EC proliferation as reflected by tritiated thymidine incorporation. Chromium 51 release assay revealed that EC viability was also unaffected by AdiNOS infection and NO synthesis. In addition, prolonged exposure to NO synthesis did not induce EC apoptosis. Instead, NO inhibited lipopolysaccharide-induced apoptosis in these cells by reducing caspase-3-like protease activity. CONCLUSIONS: Vascular iNOS gene transfer, while inhibiting smooth **muscle cell** proliferation, does not impair EC mitogenesis or viability. Augmented NO synthesis may also protect ECs against apogenic stimuli such as lipopolysaccharide. Therefore iNOS gene transfer may promote endothelial regeneration and can perhaps accelerate vascular healing.

L12 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2002 ACS
AN 1997:710292 CAPLUS
DN 127:355315
TI Adenoviral iNOS gene transfer activates cGMP- and p21-dependent antiproliferative pathways in vascular smooth **muscle cells**
SO Surgical Forum (**1997**), 48, 432-433
CODEN: SUFOAX; ISSN: 0071-8041
AU Tzeng, Edith; Lizonova, Alena; Kovesdi, Imre; Shears, Larry L., II; Billiar, Timothy R.
AB In rat aortic smooth **muscle cells**, expts. were carried out to detn. the mechanism of inhibition of proliferation by an adenoviral **vector** carrying the human inducible nitric oxide (NO) synthase (iNOS) cDNA. Both cGMP levels and p21 expression appeared to be involved in the antiproliferative actions of iNOS gene transfer on smooth **muscle cells**. However, cGMP does not appear to be involved in regulating p21 expression in response to iNOS gene transfer.

L12 ANSWER 9 OF 13 MEDLINE
AN 1999097268 MEDLINE
TI Recombination of nonreplicative RNA precursors of Sindbis virus in infected cells overexpressing murine-**inducible nitric oxide synthase**.
SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, **(1998 Dec 18)** 253 (2) 524-31.
Journal code: 0372516. ISSN: 0006-291X.
AU Herrmann A; Muller G; Godecke A; Schrader J
AB The Sindbis virus-based SINrep5 expression system is one of the most efficient **vectors** for gene transfer leading to fast and high expression of the gene of interest. This system was used to transfect vascular endothelial and smooth **muscle cells** using murine **inducible nitric oxide synthase** (miNOS) as a reporter gene. Infection of both cell types leads to high expression levels of miNOS. In addition, the harvested supernatant of these infected cells was used for further rounds of infections, demonstrating that recombination of the parental RNA with the helper RNA takes place and results in the production of infectious particles. As shown by RT-PCR, after recombination the miNOS gene is located in between the nonstructural and structural viral genes. This study demonstrates that despite claims in other publications, the Sindbis

virus-based SINrep5 expression system leads to recombination and is thus not a safe system for in vitro and in vivo applications.
Copyright 1998 Academic Press.

L12 ANSWER 10 OF 13 MEDLINE
AN 1998410903 MEDLINE
TI Efficient inhibition of intimal hyperplasia by adenovirus-mediated **inducible nitric oxide synthase** gene transfer to rats and pigs in vivo.
SO JOURNAL OF THE AMERICAN COLLEGE OF SURGEONS, **(1998 Sep)** 187 (3) 295-306.
Journal code: 9431305. ISSN: 1072-7515.
AU Shears L L 2nd; Kibbe M R; Murdock A D; Billiar T R; Lizonova A; Kovesdi I; Watkins S C; Tzeng E
AB BACKGROUND: Inadequate nitric oxide (NO) availability may underlie vascular smooth muscle overgrowth that contributes to vascular occlusive diseases including atherosclerosis and restenosis. NO possesses a number of properties that should inhibit this hyperplastic healing response, such as promoting reendothelialization, preventing platelet and leukocyte adherence, and inhibiting cellular proliferation. STUDY DESIGN: We proposed that shortterm but sustained increases in NO synthesis achieved with inducible NO synthase (iNOS) gene transfer at sites of vascular injury would prevent intimal hyperplasia. We constructed an adenoviral **vector**, AdiNOS, carrying the human iNOS cDNA and used it to express iNOS at sites of arterial injury in vivo. RESULTS: AdiNOS-treated cultured vascular smooth **muscle cells** produced up to 100-fold more NO than control cells. In vivo iNOS gene transfer, using low concentrations of AdiNOS (2 x 10(6) plaque forming units [PFU]/rat) to injured rat carotid arteries, resulted in a near complete (>95%) reduction in neointima formation even when followed longterm out to 6 weeks post-injury. This protective effect was reversed by the continuous administration of an iNOS selective inhibitor L-N6-(1-iminoethyl)-lysine. However, iNOS gene transfer did not lead to regression of preestablished neointimal lesions. In an animal model more relevant to human vascular healing, iNOS gene transfer (5 x 10(8) PFU/pig) to injured porcine iliac arteries in vivo was also efficacious, reducing intimal hyperplasia by 51.8%. CONCLUSIONS: These results indicate that shortterm overexpression of the iNOS gene initiated at the time of vascular injury is an effective method of locally increasing NO levels to prevent intimal hyperplasia.

L12 ANSWER 12 OF 13 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:459932 BIOSIS
TI Expression of **inducible nitric oxide synthase** with a novel adeno-associated virus **vector**.
SO Nitric Oxide, (1998) Vol. 2, No. 2, pp. 88.
Meeting Info.: Third International Conference on Biochemistry and Molecular Biology of Nitric Oxide Los Angeles, California, USA July 11-15, 1998 Nitric Oxide Society
. ISSN: 1089-8603.
AU Murdock, Alan (1); Krisky, D.; Billiar, T. R. (1); Xiao, X.

L12 ANSWER 13 OF 13 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:294601 BIOSIS
TI Nitric oxide synthase (NOS) gene therapy for erectile dysfunction: Comparison between **plasmid**, adenovirus and adenovirus transduced **myoblast vectors**.
SO Journal of Urology, **(May, 1998)** Vol. 159, No. 5 SUPPL., pp. 90.
Meeting Info.: 93rd Annual Meeting of the American Urological Association, Inc. San Diego, California, USA May 30-June 4, 1998 American Urological Association
. ISSN: 0022-5347.
AU Huard, Johnny; Tirney, Sean; Mattes, Carol E.; Watanabe, Toyohiko; Ozawa, Hideo; Yoshimura, Naoki; , Jose Moreno; Birder, Lori A.; Kanai, Anthony J.; Degroat, William C.; Tzeng, Edith; Kibbe, Melina; Hierholzer, Christian; Geller, David A.; Simmons, Richard L.; Billiar, Timothy R.; Chancellor, Michael B.

=>

L Number	Hits	Search Text	DB	Time stamp
1	443	inducible ADJ nitric ADJ oxide ADJ synthase	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2002/10/17 18:49
15	7	(inducible ADJ nitric ADJ oxide ADJ synthase) SAME (gene ADJ therapy)	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2002/10/17 18:56
22	2	("5594032").PN.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/10/17 18:55
28	26	(inducible ADJ nitric ADJ oxide ADJ synthase) SAME (muscle ADJ cell)	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2002/10/17 19:00
35	1	(inducible ADJ nitric ADJ oxide ADJ synthase) SAME (myoblast)	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2002/10/17 19:03
42	1	WO NEAR "9614748"	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2002/10/17 19:03
56	0	WO-9614748	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2002/10/17 19:04
75	1	WO WITH "9614748"	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2002/10/17 19:05
-	36	(urinary ADJ incontinence) and (gene ADJ therapy)	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2002/10/09 18:09
-	7	(US-5763416-$ or US-5942496-$ or US-6239117-$ or US-6271211-$).did. or (WO-9833529-$).did. or (US-6239117-$ or WO-200037124-$ or US-20010041355-$).did.	USPAT; EPO; DERWENT	2002/05/15 17:14
-	10	COLEMAN-MICHAEL	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2002/10/09 18:06
-	10	(US-5942496-$ or US-5763416-$ or US-6271211-$ or US-6239117-$ or US-5068224-$ or US-5444047-$).did. or (WO-9833529-$ or WO-9824922-$).did. or (US-20010041355-$ or US-6239117-$ or WO-200037124-$).did.	USPAT; EPO; DERWENT	2002/05/16 14:20
-	157	(IGF-I or IGF-II or (insulin ADJ like)) and (URETHERA$1 OR SPHINCTER OR DETRUSOR OR PELVIC)	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2002/05/16 14:23
-	33	((IGF-I or IGF-II or (insulin ADJ like)) and (URETHERA$1 OR SPHINCTER OR DETRUSOR OR PELVIC)) and ((atrophy or atrophied or dysfunction) SAME (muscle or muscular))	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2002/05/16 14:26

-	3691	urinary ADJ incontinence	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2002/10/09 17:59
-	2	(urinary ADJ incontinence) and (inducible ADJ nitric ADJ oxide)	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2002/10/09 18:09
-	4229	urinary WITH incontinence	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2002/10/09 17:59
-	6	(urinary WITH incontinence) and (inducible ADJ nitric ADJ oxide)	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2002/10/09 17:59
-	3	CHANCELLOR ADJ MICHAEL	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2002/10/09 18:06
-	507	inducible ADJ nitric ADJ oxide	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2002/10/09 18:09
-	75	(inducible ADJ nitric ADJ oxide) and (gene ADJ therapy)	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2002/10/09 18:10
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PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

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08/337,357 10 November 1994 (10.11.94) US

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US 08/337,357 (CIP)
Filed on 10 November 1994 (10.11.94)

(71) Applicant *(for all designated States except US)*: NIREC, INC. [US/US]; 1st floor, 11333 Iowa Avenue, West Los Angeles, CA 90025 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: GONZALEZ-CADAVID, Nestor, F. [US/US]; 3350 Calvert Road, Pasadena, CA 91107 (US). RAJFER, Jacob [US/US]; 16 Quaterhorse Lane, Rolling Hills Estates, CA 90274 (US).

(74) Agents: DULIN, Jacques, M. et al.; Pillsbury Madison & Sutro, L.L.P., Suite 800, Ten Almaden Boulevard, San Jose, CA 95113 (US).

(81) Designated States: AL, AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KP, KR, LK, LR, LT, LV, MD, MK, MX, NO, NZ, PL, RO, RU, SI, SK, TT, UA, US, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

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(54) Title: AMELIORATION OF HUMAN ERECTILE DYSFUNCTION BY TREATMENT WITH iNOS, AND RELATED NOS AGENTS

(57) Abstract

Treatment of erectile dysfunction comprising administering to a patient, inducible Nitric Oxide Synthase (iNOS) agents, including penile iNOS, inducers of penile iNOS, iNOS cDNA, or penile smooth muscle cells or corpora cavernosa with iNOS cDNA. Typical *in vivo* treatment involves delivery of these agents to the penile tissue of a patient by constant or intermittent implanted or external infusion pump, pellets, intraurethral administration, injection or other related procedures. The genetically engineered cells or penile tissue from the patient hyperexpressing iNOS is implanted in microcapsules, pellets, or other methods, or directly by surgical inoculation into the corpora cavernosa. In certain cases, an oral or injectable systemic route of administration is applicable. Also disclosed are methods of treatment involving *in vitro* induction of iNOS in cultured smooth muscle cells and thereofter delivery of purified or recombinant iNOS enzyme, production of iNOS cDNA and genetic transformation with iNOS cDNA, followed by delivery thereof to the penis of a patient. The methods of this invention include hyperexpression and/or biological modulation of other endogenous and exogenous NOS isoforms in the penis, for the treatment of erectile dysfunction.